



BILLING CODE 6560-50-P

## **ENVIRONMENTAL PROTECTION AGENCY**

### **40 CFR Part 180**

**[EPA-HQ-OPP-2017; FRL-9994-70]**

### **Nicotinamide; Exemption from the Requirement of a Tolerance**

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Final rule.

**SUMMARY:** This regulation establishes an exemption from the requirement of a tolerance for residues of nicotinamide (CAS Reg. No. 98-92-0) when used as an inert ingredient (corrosion inhibitor) on growing crops only and limited to 5.0% in a pesticide formulation. Dow AgroSciences LLC submitted a petition to EPA under the Federal Food, Drug, and Cosmetic Act (FFDCA), requesting an amendment to an existing requirement of a tolerance. This regulation eliminates the need to establish a maximum permissible level for residues of nicotinamide.

**DATES:** This regulation is effective [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Objections and requests for hearings must be received on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the **SUPPLEMENTARY INFORMATION**).

**ADDRESSES:** The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2017-0046, is available at <http://www.regulations.gov> or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to

4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at <http://www.epa.gov/dockets>.

**FOR FURTHER INFORMATION CONTACT:** Michael L. Goodis, Registration Division (7505P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; main telephone number: (703) 305-7090; email address: [RDFRNotices@epa.gov](mailto:RDFRNotices@epa.gov).

## **SUPPLEMENTARY INFORMATION:**

### **I. General Information**

#### *A. Does this Action Apply to Me?*

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

#### *B. How Can I Get Electronic Access to Other Related Information?*

You may access a frequently updated electronic version of 40 CFR part 180 through the Government Publishing Office's e-CFR site at <http://www.ecfr.gov/cgi-bin/text->

*idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab\_02.tpl.*

### *C. How Can I File an Objection or Hearing Request?*

Under FFDCA section 408(g), 21 U.S.C. 346a, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2017-0046 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing and must be received by the Hearing Clerk on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b).

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178, please submit a copy of the filing (excluding any Confidential Business Information (CBI)) for inclusion in the public docket. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit the non-CBI copy of your objection or hearing request, identified by docket ID number EPA-HQ-OPP-2017-0046, by one of the following methods:

- *Federal eRulemaking Portal*: <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be CBI or other information whose disclosure is restricted by statute.
- *Mail*: OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001.
- *Hand Delivery*: To make special arrangements for hand delivery or delivery of boxed

information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>.

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

## **II. Petition for Exemption**

In the *Federal Register* of June 8, 2017 (82 FR 26641) (FRL-9961-14), EPA issued a document pursuant to FFDCA section 408, 21 U.S.C. 346a, announcing the filing of a pesticide petition (IN-11012) by Dow AgroSciences LLC, 9330 Zionsville Road, Indianapolis, IN 46268. The petition requested that 40 CFR 180.920 be amended by establishing an exemption from the requirement of a tolerance for residues of nicotinamide (CAS Reg. No. 98-92-0) when used as an inert ingredient (corrosion inhibitor) in pesticide formulations applied to growing crops, limited to 5% in the pesticide formulation. That document referenced a summary of the petition prepared by Dow AgroSciences LLC, the petitioner, which is available in the docket, <http://www.regulations.gov>. Comments were received on the notice of filing. EPA's response to these comments is discussed in Unit V.B.

## **III. Inert Ingredient Definition**

Inert ingredients are all ingredients that are not active ingredients as defined in 40 CFR 153.125 and include, but are not limited to, the following types of ingredients (except when they have a pesticidal efficacy of their own): Solvents such as alcohols and hydrocarbons; surfactants such as polyoxyethylene polymers and fatty acids; carriers such as clay; thickeners such as carrageenan and modified cellulose; wetting, spreading, and dispersing agents; propellants in aerosol dispensers; microencapsulating agents; and emulsifiers. The term “inert” is not intended to imply nontoxicity; the ingredient may or may not be chemically active. Generally, EPA has exempted inert ingredients from the requirement of a tolerance based on the low toxicity of the

individual inert ingredients.

#### **IV. Aggregate Risk Assessment and Determination of Safety**

Section 408(c)(2)(A)(i) of FFDCA allows EPA to establish an exemption from the requirement for a tolerance (the legal limit for a pesticide chemical residue in or on a food) only if EPA determines that the tolerance is “safe.” Section 408(c)(2)(A)(ii) of FFDCA defines “safe” to mean that “there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.” This includes exposure through drinking water and in residential settings, but does not include occupational exposure. Section 408(c)(2)(B) requires EPA to take into account the considerations set forth in subparagraphs (C) and (D) of subsection (b)(2) when making this exemption safety determination. Section 408(b)(2)(C) of FFDCA requires EPA to give special consideration to exposure of infants and children to the pesticide chemical residue in establishing a tolerance and to “ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue....”

EPA establishes exemptions from the requirement of a tolerance only in those cases where it can be clearly demonstrated that the risks from aggregate exposure to pesticide chemical residues under reasonably foreseeable circumstances will pose no appreciable risks to human health. In order to determine the risks from aggregate exposure to pesticide inert ingredients, the Agency considers the toxicity of the inert in conjunction with possible exposure to residues of the inert ingredient through food, drinking water, and through other exposures that occur as a result of pesticide use in residential settings. If EPA is able to determine that a finite tolerance is not necessary to ensure that there is a reasonable certainty that no harm will result from

aggregate exposure to the inert ingredient, an exemption from the requirement of a tolerance may be established.

Consistent with FFDCA section 408(c)(2)(A), and the factors specified in FFDCA section 408(c)(2)(B), EPA has reviewed the available scientific data and other relevant information in support of this action. EPA has sufficient data to assess the hazards of and to make a determination on aggregate exposure for nicotinamide including exposure resulting from the exemption established by this action. EPA's assessment of exposures and risks associated with nicotinamide follows.

#### *A. Toxicological Profile*

EPA has evaluated the available toxicity data and considered their validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. Specific information on the studies received and the nature of the adverse effects caused by nicotinamide as well as the no-observed-adverse-effect-level (NOAEL) and the lowest-observed-adverse-effect-level (LOAEL) from the toxicity studies are discussed in this unit.

Nicotinamide is a water-soluble B-complex vitamin which is present naturally in animal products, whole cereals and legumes. Together with nicotinic acid (niacin), nicotinamide belongs to vitamin B3 and is required as a nutrient to prevent niacin deficiency disorders such as pellagra. It functions as a coenzyme or co-substrate in many biological reduction and oxidation reactions required for energy metabolism in mammalian systems. It is used as a nutritional supplement, therapeutic agent, skin and hair conditioning agent in cosmetics and a constituent of consumer, household solvent and cleaning products.

As a nutritional supplement and vitamin, recommended daily dietary allowances and maximum daily doses have been established by the Institute of Medicine (US) Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline. The committee also established the tolerance upper intake level at 35 mg/day based on flushing as a critical adverse effect. The level applies to all forms of niacin added to foods or taken as supplements, including nicotinamide. Although nicotinamide is not associated with flushing effects, a UL for nicotinic acid based on flushing is protective against the other effects seen in the available toxicity studies.

Nicotinamide exhibits low levels of acute toxicity. The rat acute oral lethal dose (LD<sub>50</sub>) is 3,000-7,000 milligrams/kilogram (mg/kg). The acute dermal LD<sub>50</sub> for rabbits is > 2,000 mg/kg. Nicotinamide is negative for skin sensitization in the guinea pig. It is not irritating to rabbit skin. Nicotinamide is considered irritating to rabbit eyes.

In a 4-week oral toxicity via gavage, no adverse effects were observed in female rats at dose levels below treated with 1,000 mg/kg/day of nicotinamide.

In a developmental toxicity study involving exposure to nicotinic acid, no effects in the dams (decreased body weight gains and significantly decreased placental weights) and fetuses (significantly lower body weights in male offspring) were observed at dose levels below 1,000 mg/kg/day. The NOAEL for maternal and developmental toxicity is 200 mg/kg/day (198 mg/kg/day for nicotinamide). This study is deemed relevant to the assessment of nicotinamide since nicotinamide converts to nicotinic acid in the gut.

Nicotinamide was negative in Ames tests, micronucleus tests, with and without metabolic activation. No chromosomal effects were reported in mammalian cells. Positive results were seen in a sister chromatid exchange induction study. However, it was noted that activity was

only seen at excessively high concentrations. Based on the weight of evidence, nicotinamide is considered negative for mutagenicity.

Nicotinamide is not carcinogenic. No increased incidence of tumors was observed in a lifetime carcinogenicity study with Swiss mice receiving 1.0% (equivalent to 66.3 and 100 mg/kg/day in female and male rats, respectively) nicotinamide in the diet.

There were no data directly regarding the potential for neurotoxicity or immunotoxicity of nicotinamide. However, there is no evidence of potential neurotoxicity or immunotoxicity in the available data.

Metabolism of nicotinamide in humans is well understood. Nicotinamide is necessary for lipid metabolism, tissue respiration and glycogenolysis. It is readily absorbed in the gastrointestinal (g.i.) tract. *In vivo*, nicotinamide is formed from the conversion of nicotinic acid (niacin), while some dietary nicotinamide is oxidized to nicotinic acid and then to nicotinamide. Nicotinamide is incorporated into two coenzymes: nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) which act as hydrogen-carrier molecules in glycogenolysis, tissue respiration and lipid metabolism. It can be incorporated into NADP either directly or after deamidation, or metabolized in the liver and excreted in the urine. The primary metabolites are N-methylniacinamide and N-methyl-2-pyridone-5- carboxamide, though it may also be excreted unchanged.

#### *B. Toxicological Points of Departure/Levels of Concern*

Once a pesticide's toxicological profile is determined, EPA identifies toxicological points of departure (POD) and levels of concern to use in evaluating the risk posed by human exposure to the pesticide. For hazards that have a threshold below which there is no appreciable risk, the toxicological POD is used as the basis for derivation of reference values for risk assessment.

PODs are developed based on a careful analysis of the doses in each toxicological study to determine the dose at which the NOAEL and the LOAEL are identified. Uncertainty/safety factors are used in conjunction with the POD to calculate a safe exposure level - generally referred to as a population-adjusted dose (PAD) or a reference dose (RfD) - and a safe margin of exposure (MOE). For non-threshold risks, the Agency assumes that any amount of exposure will lead to some degree of risk. Thus, the Agency estimates risk in terms of the probability of an occurrence of the adverse effect expected in a lifetime. For more information on the general principles EPA uses in risk characterization and a complete description of the risk assessment process, see <http://www.epa.gov/pesticides/factsheets/riskassess.htm>.

The available toxicity studies indicate that nicotinamide has a very low overall toxicity. No effects are observed below 1,000 mg/kg/day, the limit dose. Since signs of toxicity were not observed below the limit dose an endpoint of concern for risk assessment purposes was not identified.

### *C. Exposure Assessment*

1. *Dietary exposure from food and feed uses.* In evaluating dietary exposure to nicotinamide, EPA considered exposure expected under the proposed exemption from the requirement of a tolerance as well as from the existing approved uses. EPA assessed dietary exposures from nicotinamide in food as follows:

Nicotinamide is already approved for use (synergist) on growing crops. The current request (for use as a corrosion inhibitor) increases dietary exposure (food and drinking water) to nicotinamide that can occur following ingestion of foods with residues from treated crops. In addition, dietary exposure to nicotinamide may also occur through foods that contain it naturally, such as grains, meat and milk; fortified foods, and dietary supplements. However, a quantitative

dietary exposure assessment was not conducted since a toxicological endpoint for risk assessment was not identified.

2. *Dietary exposure from drinking water.* Since a hazard endpoint of concern was not identified for the acute and chronic dietary assessment, a quantitative dietary exposure risk assessment for drinking water was not conducted, although exposures may be expected from use on food crops.

3. *From non-dietary exposure.* The term “residential exposure” is used in this document to refer to non-occupational, non-dietary exposure (e.g., textiles (clothing and diapers), carpets, swimming pools, and hard surface disinfection on walls, floors, tables).

Nicotinamide may be used as an inert ingredient in pesticide products that are registered for specific uses that may result in residential exposure, such as pesticides used in and around the home, and in non-pesticide products such as household products, personal care products and cosmetics. However, based on the lack of a hazard endpoint of concern, a quantitative residential exposure assessment for nicotinamide was not conducted.

4. *Cumulative effects from substances with a common mechanism of toxicity.* Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider “available information” concerning the cumulative effects of a particular pesticide's residues and “other substances that have a common mechanism of toxicity.”

EPA has not found nicotinamide to share a common mechanism of toxicity with any other substances, and nicotinamide does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that nicotinamide does not have a common mechanism of toxicity with other substances. For

information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see EPA's website at <http://www.epa.gov/pesticides/cumulative>.

#### *D. Safety Factor for Infants and Children*

Based on the lack of threshold effects, EPA has not identified any toxicological endpoints of concern and is conducting a qualitative assessment of nicotinamide. The qualitative assessment does not use safety factors for assessing risk, and no additional safety factor is needed for assessing risk to infants and children. Based on an assessment of nicotinamide, EPA has concluded that there are no toxicological endpoints of concern for the U.S. population, including infants and children.

#### *E. Aggregate Risks and Determination of Safety*

Because no toxicological endpoints of concern were identified, EPA concludes that aggregate exposure to residues of nicotinamide will not pose a risk to the U.S. population, including infants and children, and that there is a reasonable certainty that no harm will result to the general population, or to infants and children from aggregate exposure to nicotinamide residues.

### **V. Other Considerations**

#### *A. Analytical Enforcement Methodology*

An analytical method is not required for enforcement purposes since the Agency is establishing an exemption from the requirement of a tolerance without any numerical limitation.

#### *B. Response to Comments*

Two comments were received concerning the safety and impact of pesticides on food and human health. Although the Agency recognizes that some individuals believe that no residue of

pesticides should be allowed in or on food, the existing legal framework provided by section 408 of the FFDCA authorizes the establishment of pesticide tolerances or exemptions where the Agency determines that tolerance or exemption meets the safety standard imposed by the statute. EPA has sufficient data to support a safety determination for the exemption from the requirement of a tolerance for nicotinamide. The commenters have provided no additional information supporting a determination that the exemption is not safe.

## **VI. Conclusions**

Therefore, an exemption from the requirement of a tolerance is established under 40 CFR 180.920 for nicotinamide (CAS Reg. No. 98-92-0) when used as an inert ingredient (corrosion inhibitor) in pesticide formulations applied to growing crops, limited to 5.0% in a pesticide formulation.

## **VII. Statutory and Executive Order Reviews**

This action establishes a tolerance exemption under FFDCA section 408(d) in response to a petition submitted to the Agency. The Office of Management and Budget (OMB) has exempted these types of actions from review under Executive Order 12866, entitled “Regulatory Planning and Review” (58 FR 51735, October 4, 1993). Because this action has been exempted from review under Executive Order 12866, this action is not subject to Executive Order 13211, entitled “Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use” (66 FR 28355, May 22, 2001); Executive Order 13045, entitled “Protection of Children from Environmental Health Risks and Safety Risks” (62 FR 19885, April 23, 1997); or Executive Order 13771, entitled “Reducing Regulations and Controlling Regulatory Costs” (82 FR 9339, February 3, 2017). This action does not contain any information collections subject to OMB approval under the Paperwork Reduction Act (PRA) (44 U.S.C. 3501 *et seq.*), nor does it

require any special considerations under Executive Order 12898, entitled “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations” (59 FR 7629, February 16, 1994).

Since tolerances and exemptions that are established on the basis of a petition under FFDCA section 408(d), such as the exemption in this final rule, do not require the issuance of a proposed rule, the requirements of the Regulatory Flexibility Act (RFA) (5 U.S.C. 601 *et seq.*), do not apply.

This action directly regulates growers, food processors, food handlers, and food retailers, not States or tribes, nor does this action alter the relationships or distribution of power and responsibilities established by Congress in the preemption provisions of FFDCA section 408(n)(4). As such, the Agency has determined that this action will not have a substantial direct effect on States or tribal governments, on the relationship between the national government and the States or tribal governments, or on the distribution of power and responsibilities among the various levels of government or between the Federal Government and Indian tribes. Thus, the Agency has determined that Executive Order 13132, entitled “Federalism” (64 FR 43255, August 10, 1999) and Executive Order 13175, entitled “Consultation and Coordination with Indian Tribal Governments” (65 FR 67249, November 9, 2000) do not apply to this action. In addition, this action does not impose any enforceable duty or contain any unfunded mandate as described under Title II of the Unfunded Mandates Reform Act (UMRA) (2 U.S.C. 1501 *et seq.*).

This action does not involve any technical standards that would require Agency consideration of voluntary consensus standards pursuant to section 12(d) of the National Technology Transfer and Advancement Act (NTTAA) (15 U.S.C. 272 note).

## **VIII. Congressional Review Act**

Pursuant to the Congressional Review Act (5 U.S.C. 801 *et seq.*), EPA will submit a report containing this rule and other required information to the U.S. Senate, the U.S. House of Representatives, and the Comptroller General of the United States prior to publication of the rule in the *Federal Register*. This action is not a “major rule” as defined by 5 U.S.C. 804(2).

**List of Subjects in 40 CFR Part 180**

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: September 11, 2019.

**Michael Goodis,**

*Director, Registration Division, Office of Pesticide Programs.*

Therefore, 40 CFR chapter I is amended as follows:

**PART 180--[AMENDED]**

1. The authority citation for part 180 continues to read as follows:

**Authority:** 21 U.S.C. 321(q), 346a and 371.

2. In §180.920, revise the inert ingredient “Nicotinamide (CAS Reg. No. 98-92-0)” in the table to read as follows:

**§ 180.920 Inert ingredients used pre-harvest; exemptions from the requirement of a tolerance.**

\* \* \* \* \*

<b>Inert ingredients</b>	<b>Limits</b>	<b>Uses</b>
<b>**</b>	<b>***</b>	<b>**</b>
Nicotinamide (CAS Reg. No. 98-92-0)	Not to exceed 0.5% by weight of pesticide formulation as synergist; not to exceed 5% by weight of pesticide formulation as corrosion inhibitor	Synergist, Corrosion Inhibitor
<b>**</b>	<b>***</b>	<b>**</b>

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